REMARKS

Claims 74-93 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Priority Data

The Office Action points out that USPTO internal records refers to patent case serial No. 09/256,377 filed 2/24/1999, now abandoned, which appears to be a Continuation In Part of case serial No. 09/031,442, filed 2/26/1998 which is now U.S. Patent No. 5,955,310, but the former case has a totally different title than this invention and Applicant is advised to clarify the priority data of the instant case in response to this Office Action.

Applicant inadvertently transcribed the wrong serial number which has now been corrected in this Amendment. The titles of all applications/patents are the same.

II. The Rejection of Claims 74-77, 80, 82-84, 86-93 under 35 U.S.C. § 103

Claims 74-77, 80, 82-84, and 86-93 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136, 1989) in view of Lereclus *et al.* (WO 94/25612) for the reasons of record. This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966).

Under 35 U.S.C. § 103, the law requires, when relying on a combination of prior art references to render a claimed invention obvious, that the prior art references contain within them a suggestion of the possibility of achieving the improvement of the claimed invention, such a suggestion being either express or implied. In re Sernaker, 217 USPQ 1 (Fed. Cir. 1983). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. Carella v. Starlight Archery, 231 USPQ 644 (Fed. Cir. 1986); In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). It is also impermissible to use the claims as a framework from which to pick and choose among individual references to recreate the

claimed invention. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). A reference, or references, must show or suggest the properties and results of the claimed invention, or suggest the claimed combination as a solution to a given problem, in order to successfully be relied upon for an obviousness rejection. In re Wright, 6 USPQ2d 1959 (Fed. Cir. 1988). The mere fact that prior art references could be readily modified to form the claimed invention is not sufficient either, since the mere fact that the prior art could be modified would not make the modification obvious unless the prior art suggests the desirability of the modification. In re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989). Applicant maintains its position that the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejections of the present claims.

Hung *et al.* teach a *Bacillus subtilis* cell comprising a DNA construct comprising a consensus *bla* promoter originated from *E. coli*, having the sequence TTGACA for the -35 region and TATAAT for the -10 region operably linked to a mouse dihydrofolate reductase (DHFG) encoding gene. Hung *et al.* do not teach or suggest a DNA construct further comprising an mRNA processing/stabilizing sequence.

Lereclus *et al.* teach an expression system comprising a CryIIIA gene, under the control of a *cryIIIA* promoter as well as a *cryIIIA* sequence called the "downstream region" or a "mRNA processing/stabilizing sequence", situated between the promoter and the coding sequence to be expressed and susceptible of acting at the post-transcriptional level during gene expression.

The Office found Applicant's arguments of February 28, 2005, unpersuasive because "it appeared that Applicant may have misunderstood the data presented in Figures 5-6 of Lereclus patent." The Office states: "Applicant is respectfully requested to read column 12 of said U.S. Patent wherein the details of plasmids construction are discussed. Based on the details provided both pHT304'lacZ and pHT7901'lacZ lack promoters. Thus, in the latter construct even though the "downstream region" is present, said region could not enhance lacZ expression because it can only act in the presence of a promoter. In Figure 6, once a promoter, which in this case happens to be a cryIIIA promoter, is present together with the 'downstream region' the lacZ expression is significantly enhanced. Hence, Figure 5 of Lereclus does not provide neqative effects of placing 'downstream region' downstream of lacZ promoter, on lacZ expression." We respectfully disagree with the Office's statement.

Plasmid pHT304'lacZ does not lack a lacZ promoter. Column 12, lines 51-55 states: "The plasmid pHT304'lacZ used to construct the transcriptional fusions was obtained by cloning the 3.2 kb DraI-SmaI restriction fragment containing the lacZ gene lacking a promoter isolated from pMC11, at the unique SmaI site of pHT304." pHT304 is shown in Figure 1A of U.S. Patent No. 6,140,104. The unique SmaI site is located downstream of the lacZ

promoter (lacZp) of pHT304. Consequently, pHT304'lacZ contains the lacZ promoter.

Plasmid pHT7901'lacZ does not lack a lacZ promoter. Column 12, lines 51-55 states: "The plasmid pHT7901'lacZ was obtained by cloning the H_3-P_1 fragment {(HindIII-PstI) see FIG. 3A} between the unique HindIII and PstI sites of pHT304'lacZ." Consequently, pHT304'lacZ also contains the lacZ promoter (lacZp).

Based on the methods described in WO 94/25612 to construct these two plasmids, it is apparent that the promoter for the *lacZ* gene is indeed present and oriented such that the *lacZ* gene is expected to be transcribed from this promoter. Indeed, Figure 5 demonstrates low levels of lacZ expression in a strain harboring pHT304'lacZ. However, there is no evidence for improvement in a strain harboring pHT901'lacZ which has the *cryIIIA* "downstream region" situated downstream of the *lacZ* promoter. One of ordinary skill in the art would expect to see a significant improvement if, in fact, a heterologous promoter is able to function in association with the *cryIIIA* "downstream region" and Figure 5 does not support this assumption. While Lereclus *et al.* show in Figure 6 of WO 94/25612 that the pHT7902'lacZ construct (where the *cryIIIA* promoter is upstream of the *cryIIIA* "downstream region" which is upstream of the *lacZ* gene) increases expression of the *lacZ* gene relative to the pHT7907'lacZ construct (where the *cryIIIA* "downstream region" is absent), no evidence is presented that the *cryIIIA* "downstream region" can be used with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. In fact, based on the results of Lereclus *et al.*, the *cryIIIA* "downstream region" appears to be specific for the *cryIIIA* promoter. Lereclus *et al.* provide no evidence that the *cryIIIA* "downstream region" can be used with any other promoter including a consensus promoter other than the *cryIIIA* promoter to increase the expression of a gene.

A valid case of *prima facie* obviousness requires that there must be a reasonable expectation of success found in the prior art. The "reasonable expectation of success" requirement has two distinct components. First, the guidance the reference provides must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the invention. The prior art does not satisfy this requirement if it is necessary to vary all parameters, or to try each of numerous possible choices, in order possibly to arrive at a successful result. The second and related element of a reasonable expectation of success is that the prior art suggesting the desirability of the invention must enable one of ordinary skill in the art to produce it.

Applicant submits that both elements of a reasonable expectation of success are lacking in the cited references. First, the references, alone or in combination, provide no guidance to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. Lereclus *et al.* presents no evidence that

the *cryIIIA* "downstream region" can be used with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. The lacZ promoter in combination with the *cryIIIA* "downstream region" did not have a positive effect of increasing expression of the lacZ gene. Consequently, one skilled in the art must to try each of numerous possible choices, in order possibly to arrive at a successful result. Second, the references, alone or in combination, do not enable one of ordinary skill in the art to produce the claimed invention. Lereclus *et al.* has not demonstrated that the *cryIIIA* "downstream region" can be used with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene.

As the record states, Applicant submits that the results of Lereclus showing that placing the *cryIIIA* "downstream region" downstream of the *lacZ* promoter has no positive effect on expression of the *lacZ* gene teaches away from using the *cryIIIA* "downstream region" with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. Based on the Lereclus results, there is no reasonable expectation of success of using the *cryIIIA* "downstream region" with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene.

Applicant maintains its position that the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejection of the present claims. Moreover, there is no motivation to inserting the "downstream region" of Lereclus *et al.* into the DNA construct of Hung *et al.* because there is no reasonable expectation of success of increasing expression of a gene based on the results obtained by Lereclus *et al.* wherein the mRNA processing/stabilizing sequence is foreign to the "consensus" promoter.

For the foregoing reasons, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 89-90 under 35 U.S.C. § 103

Claims 89-90 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus *et al.* (WO 94/25612) further in view of Jorgensen *et al.* (WO 93/10249) for the reasons of record. This rejection is respectfully traversed.

Hung *et al.* and Lereclus *et al.* are discussed in Section II above.

Jorgensen *et al.* disclose a *Bacillus* promoter derived from a variant of a *Bacillus licheniformis* alpha-amylase promoter for use in expressing heterologous genes.

For the reasons stated in Section II, Applicant submits that the rejections under 35

U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

IV. The Rejection of Claim 78 under 35 U.S.C. § 103

Claim 78 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus (WO 94/25612) further in view of Diderichsen (*Res. Microbiol.* 142: 7-8, 793-96, 1991). The Office Action states:

> At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the Bacillus host harboring the construct of Hung in view of Lereclus and replace the promoter of said construct with that of Diderichsen in order to enhance expressing of any exogenous enzyme expressing gene including the alpha-amylase of Diderichsen. One of ordinary skill in the art is motivated in expressing amyS of Diderichsen at high quantities using amyQ promoter of Diderichsen in the construct and Bacillus of Hung in view of Lereclus because Diderichsen specifically teaches that thermostable alpha amylase is used for industrial production of glucose or high fructose syrups in food industry. Finally, one of ordinary skill in the art has a reasonable of expectation of success in expressing high levels of alpha amylase because Lereclus teaches that amylase promoters may be successfully used in its constructs (see column 5 of U.S. Patent 6,140,104) and Diderichsen displays positive results when amyQ promoters were used in expression of amyS in B. substillis host cells rendering the invention obvious.

This rejection is respectfully traversed.

Hung *et al.* and Lereclus *et al.* are discussed in Section II above.

Diderichsen discloses using *amyQ* and *amyM* promoters in enhancing expression of a *Bacillus stearothermophilus* alpha-amylase (*amyS*) gene in *Bacillus subtillis* and displays 3-fold increase in *amyS* productivity compared to an equivalent *B. subtillis* construction.

For the reasons stated in Section II, Applicant submits that the rejection under 35 U.S.C. § 103(a) has been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

V. The Rejection of Claim 85 under 35 U.S.C. § 103(a)

Claim 85 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus (WO 94/25612) further in view of Jorgensen (WO 96/23073). The Office Action states:

> At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the Bacillus cell of Hung in view of Lereclus and delete the selectable markers of the construct comprised therein, according to Jorgensen* such that plasmids of said Bacillus may be used for homologous recombination into chromosome of sad Bacillus or other species of Bacillus family.
>
> One of ordinary skill in the art would be motivated to delete selectable marker genes of such plasmid comprised in Bacillus of Hung in view of

Lereclus according to Jergensen because Jergensen teaches that the presence of such marker genes in chromosome of a Bacillus host cell are undesirable from an a environmental and product approval point of view (see page 4).

Finally, one of ordinary skill in the art has a reasonable expectation of success in preparing such Bacillus host because Jergensen has successfully prepared and claimed (see claim 30) such cell prior to this invention rendering the invention obvious.

This rejection is respectfully traversed.

Hung *et al.* and Lereclus *et al.* are discussed in Section II and Jorgensen in Section II above.

For the reasons stated in Section II, Applicant submits that the rejection under 35 U.S.C. § 103(a) has been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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Robert L. Starnes, Ph.D.
Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
530-757-8100
530-757-4715 (direct)